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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,660	12/22/1998	EVAN C. UNGER	UNGR-1520	2775

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WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE, 46TH FLOOR
1650 MARKET STREET
PHILADELPHIA, PA 19103

EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/218,660	UNGER ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100, 102, 127, 194-200, 203, 210-213, 217-228, 294-300, 303, 310-329, 331-337, 347-356, 412* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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Continuation of Disposition of Claims: Claims pending in the application are 100,102,127,194-200,203,210-213,217-228,294-300,303,310-329,331-337,347-356 and 412.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 27, 2005, and October 10, 2004 have been entered.

Claims 100, 102, 127, 194-200, 203, 210-213, 217-228, 294-300, 303, 310-329, 331-337, 347-356, 412 are pending.

Priority

2. The effective priority date used for the examination of the instant application is May 1, 1996.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 100, 102, 127, 194-200, 203, 210-213, 217-228, 294-300, 303, 310-329, 331-337, 347-356, 412 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant generic claims 100, 127, 412 and the dependent claims thereof contain the limitation "solid membrane" which renders the claimed invention ambiguous. Specifically, the scope of such limitation is not clear within the context of the entire

claim. The term solid generally means ""not hollowed" or "having a definite configuration." (see Webster II, page 1106). However, the pending claims are not only directed to bubble type vesicles having internal voids, but also liposomes (see for example claim 102) which are flexible cell-like structures enclosing an aqueous compartment. Thus, the nature of the formulation can hardly be characterized as solid. Examiner requests clarification of the scope of the term "solid" and "solid membrane" within the context of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 100, 102, 127, 194-200, 203, 210-213, 217-220, 294-300, 303, 310-317, 326, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen US

Patent 5,620,689 (Allen) in view of Wallach US Patent 4,853,228 (Wallach), Schneider US Patent 5,643,553 (Schneider) and Porter US Patent 5,648,098 (Porter).

The instant claims are directed toward methods of use and formulation comprising targeted phospholipid containing vesicles comprising a substantially insoluble gas, a linking group and a targeting ligand, wherein the linking group is a hydrophilic polymer that is covalently bound to both the surface of the lipid vesicle and said targeting ligand and is selected from a group consisting of PEG, polypropylene glycol, polyvinylalcohol. PVP, and copolymers thereof and wherein the vesicle is free of disulfide linkage.

Allen discloses methods of treating patients with targeted liposomes. (abstract, col 29, lines 2-30). Allen's composition comprising lipid vesicles such as liposomes which are used for delivery of diagnostic or therapeutic agents. Allen discloses that the liposomes shells may be formed from a phospholipid such as PE, (see entire col 6-8). Examiner has interpreted the instant recitation "solid membrane" to mean a continuous layer. Allen's shells are viewed to fall within the instant limitation "solid membrane," because liposomes of Allen comprise a continuous lipid bilayer film (abstract, col 10, lines 55-67). Thus, Attached to the vesicle shell is a polymer chain of PEG having a molelular weight org between 500-10000 dalton which is attached covalently to an antibody (see col 2, lines 55-66; col 5-6; fig. 1, col 11, lines 38-66; col 12, lines 29-34). Allen's liposomes contain entrapped therapeutic agents and imaging agents (see col 7, lines 30-55). Allen does not teach gas-containing vesicles.

Wallach's teachings are complementary to Allen's as it explicitly describes the covalent bonding between the linker, targeting agent and the phospholipids moiety of a liposomal shell. Wallach discloses a composition comprising lipid vesicles such as liposomes for delivery of contrast agents and therapeutic agents (see col 5, lines 8-30; col 10, lines 10-42). Wallach teaches that his lipid vesicles can be conjugated to targeting ligands such as peptides to provide the advantage of in vivo site specificity (see col 4, lines 61+). Wallach's compositions comprise a lipid bilayer vesicles having a targeting moiety and a polymeric surfactant. (see col 9, lines 10-36). Wallach specifically teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7). The vesicles of Wallach do not contain a disulfide linkage. Wallach only fails teach liposome containing a gaseous ultrasound contrast agent.

The use of gaseous perfluorocarbons in combination with drug delivery vesicles has been well established in the art. Schneider for example teaches liposomal composition comprising gas-filled microbubbles, wherein the microbubbles may contain various surfactant such as a microbubble shell forming phospholipid or more specifically PE, as well as, polymeric surfactants, such as PEG surfactants, (col 6, lines 25-64; claims 4-20). Schneider also teaches that targeting ligands (e.g, polypeptides, antibodies, etc..) may be bounded by the stabilizing surfactant layer of the microbubbles to provide site-specific targeting of the diagnostic or therapeutic microbubbles (see col 9, lines 10 +, example 11). Thus, Schneider teaches microbubbles that comprise PE

shells combined with a PEG surfactant, which may be bound with a peptide targeting ligand. Schneider does not explicitly teach a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker.

However, Porter teaches method of improving drug activity when microvesicles contains perfluorocarbon gas, which cavitate in the presence of an ultrasound field. (see abstract; col 8, lines 19-45). Porter specifically exemplifiy perfluorobutane as a suitable gas. (see col 8, lines 38-42).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to further incorporate a gaseous ultrasound contrast agent of Schneider in the liposomes of Allen and Wallach and use such formulations for therapeutic or diagnostic purposes, because as suggested by both Allen and Wallach, the liposomes can contain a contrast agent. Further, the ordinary skill in the art would have had a reasonable expectation of success to use a perfluorcarbon gaseous contrast agents in the liposomes of Wallach and Allen, because as taught by Schneider and Porter, gaseous vesicles, specifically perflourocarbon gases such as perfluorobutane, improve drug delivery of a therapeutic agent to a site of interest.

4. Claims 318-325, 327-329, 331-337, 347-356 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen in view of Wallech, Schneider and Porter as applied to claims 100, 102, 127, 194-200, 203, 210-213, 217-220, 294-300, 303, 310-317, 326, 412 and further in view of Ginsburg US Patent 5,656,442 (Ginsburg).

The combination of Allen, Wallach, Schneider and Porter are described above. Such combination does not teach the specific targeting group of Arg-Gly-Asp ("RGD") or Lys-Gln-Ala-Gly-Asp-Val.

Ginsburg discloses the synthetic alpha-amino acid containing chains of Lys-Gln-Ala-Gly-Asp-Val or RGD (col 33, lines 45-55). Ginsburg further teaches that such amino-acid chains specifically bind to fibrinogen of the platelet membrane glycoprotein complex IIb/IIIa receptor and that they can be used as a targeting ligand in an in vitro kit (abstract).

Although the combination of the teachings of Allen, Wallach, Schneider and Porter does not specifically teach the use of Lys-Gln-Ala-Gly-Asp-Val or RGD as a targeting agent, they suggest the use of any suitable targeting agent to improve specificity of their drug delivery system.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to use a suitable targeting agent such as those taught by Ginsburg, because the ordinary artisan would have had a reasonable expectation of success to improve specificity of a drug delivery vesicles to platelet membranes when employing Ginsburgs' targeting agents.

Response to Arguments

5. Applicant's arguments filed October 05, 2004 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant has argued that Schneider does not teach the instant "solid phopholipid" membrane in his vesicles. As reasoned above, the shortcomings of Schneider cannot be the basis of nonobviousness, because the rejection is based on the teachings of the combined references. Further, the pending rejection employs Allen as the primary reference. Allen clearly shows a phospholipids membrane entrapping the therapeutic agents, thus, teaching the argued limitation. Schneider is merely used as a secondary reference to show the state of art as to application of a gaseous contrast agent in combination with a liposome containing therapeutic agent. Accordingly, Applicant's arguments are not on point and thus not persuasive.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER